

Guidelines for Short-Course Treatment of LTBI

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Disclosures

- ❑ No relevant financial disclosures
- ❑ Other than isoniazid, none of the drugs I mention are FDA-approved for any of the indications in this presentation.



John Snow

- ❑ 1954 cholera outbreak in London
- ❑ Identified a single water pump as the source of the outbreak
- ❑ Epidemic abated after the pump handle was removed
- ❑ Later showed that the water company was pumping sewage from the Thames to the affected area



\$9.56 at Home Depot

TB in the U.S.

□ Active TB (2010 data)

- 11,182 cases
- 3.6 cases per 100,000
- 547 deaths (2009)

CDC. *Reported Tuberculosis in the United States, 2010*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2011.

1999-2000 National Health and Nutritional Examination Survey

□ LTBI prevalence (TST > 10mm):

Bennett DE. *Am J Respir Crit Care Med*. 2008 Feb 1;177(3):348-55

- 4.2% = 11,213,000 persons infected
 - 1.8% in U.S.-born
 - 18.7% in foreign-born
- 25.5% reported prior history of TB/LTBI
 - Only 13.2% reported prior treatment (about half)

□ Goal for 2010* = incidence of 1 per 1,000,000 for active cases (MMWR. 1989 Jan 13;38(1):1-4)

- Requires LTBI prevalence of 1% or less
Styblo K. *Bull Int Union Tuberc Lung Dis* 1990;65:49-55

*Per CDC's Healthy People 2010. TB is not mentioned in Healthy People 2020.

Why do we treat LTBI?

- ☐ Prevent deaths
 - People still die from TB
- ☐ Prevent morbidity
 - Especially in kids
- ☐ Save money
 - It costs less to treat LTBI than active TB

Why do we treat LTBI?

- ☒ ~~Prevent deaths~~
 - ~~■ People still die from TB~~
- ☒ ~~Prevent morbidity~~
 - ~~■ Especially in kids~~
- ☐ **Save money**

(But lives are also important.)

What does treating LTBI cost?

□ Several costs to consider:

- Drugs
- Nursing time
- Monitoring
- Toxicity
- DOT

□ But also savings:

- Cases averted
- Secondary cases averted
 - (Remember: Infectious diseases are *infectious*)

LTBI treatment – susceptible disease

Recommended regimens

Drug	Frequency	Duration	Issues	Abbrev
Isoniazid	Daily	9 months (6 months)	Long duration, poor adherence	9H
Isoniazid	Twice weekly	9 months (6 months)	Directly-observed, long duration	9H-DOT
Rifampin	Daily	4 months	Drug interactions	4R

Other regimens

Isoniazid + rifapentine	Once weekly	3 months	Experimental, DOT	3HP
Rifampin + pyrazinamide	Daily or 2x/week	2 months	Potentially fatal	2RZ
Isoniazid + rifampin	Daily	3 months	Not in U.S. recommendations	3HR

Isoniazid for LTBI

- ❑ Dozens of studies on efficacy
- ❑ Cheap
- ❑ Current standard of care
- ❑ Nine months recommended for all groups

Isoniazid

Risk reduction from various durations of INH
in patients with LTBI.

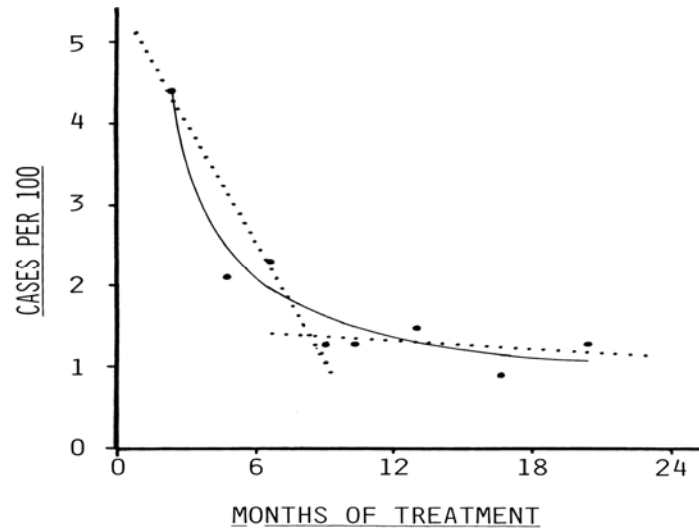
Bull. World Health Organ. 1982;60(4):555-64.

Duration (months)			
Group	3	6	12
Overall	21%	65%	75%
Completer/compliers	31%	69%	93%

A subsequent cost-effectiveness analysis showed 6H to
be more cost-effective than 12H.

Snider DE. JAMA. 1986 Mar 28;255(12):1579-83.

Isoniazid for nine months



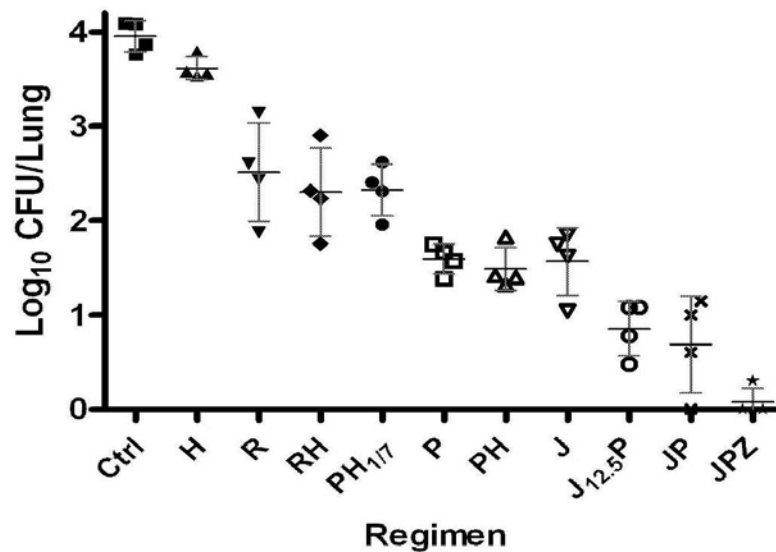
Comstock GW. *Int J Tuberc Lung Dis.* 1999 Oct;3(10):847-50.

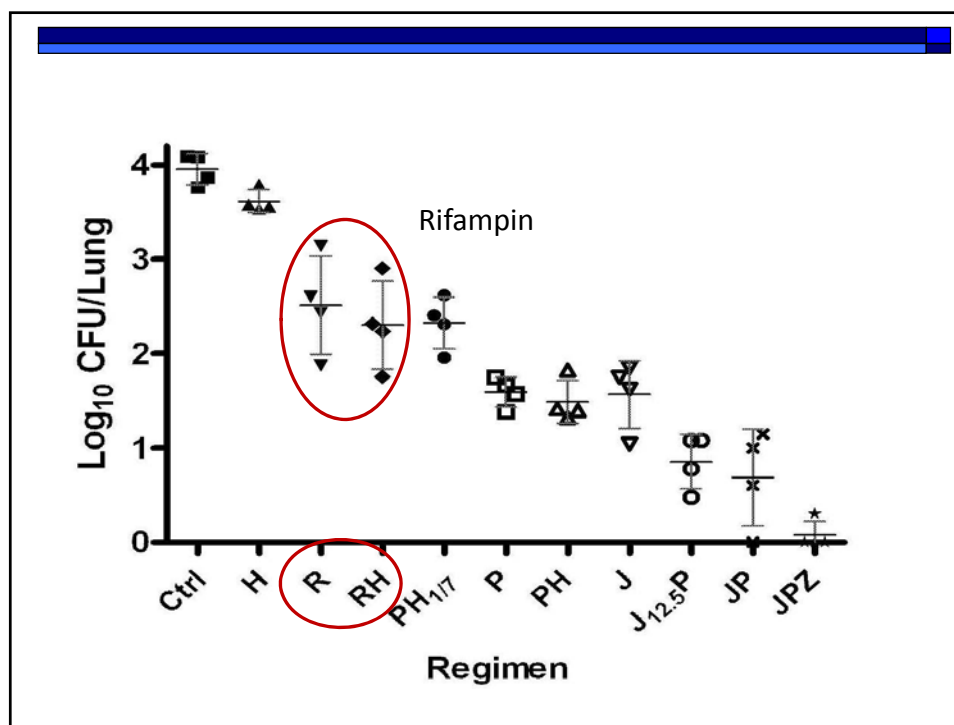
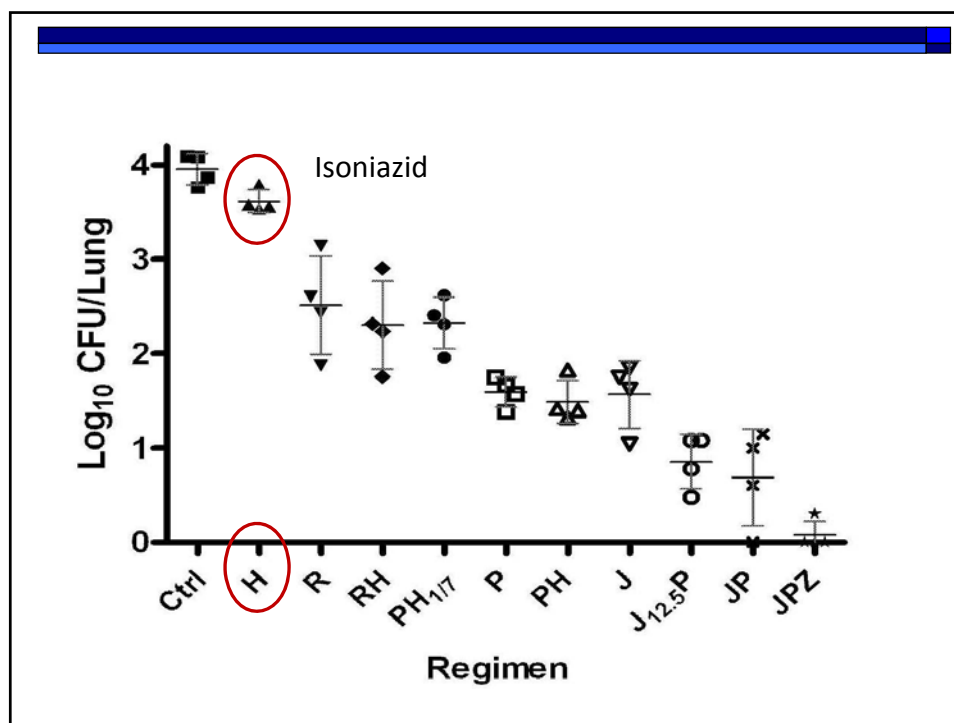
Problems with isoniazid

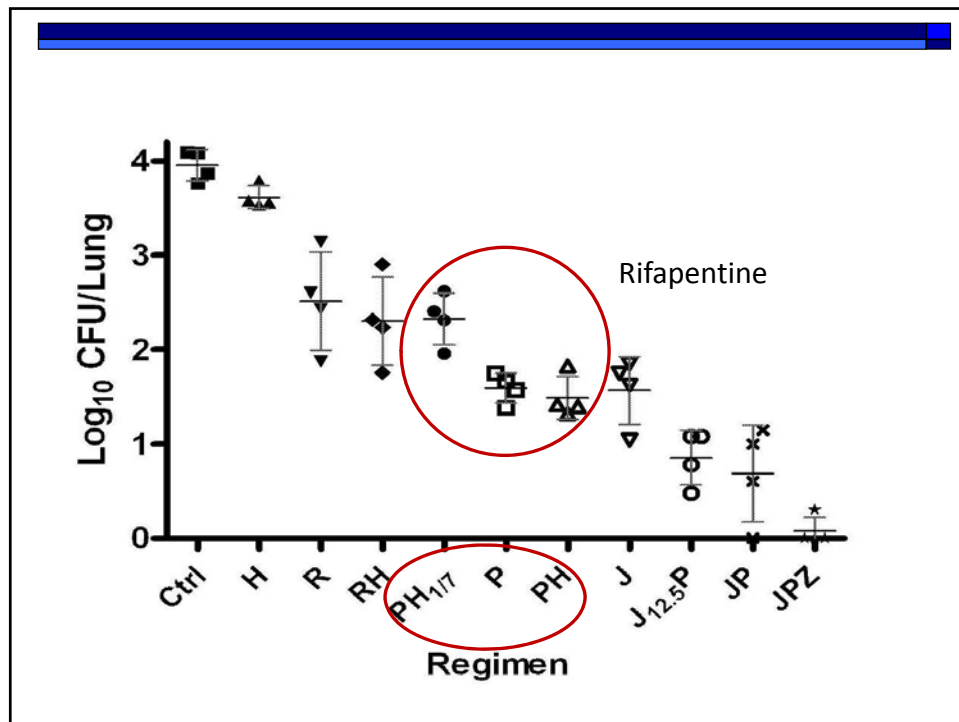
- Poor adherence
 - Completion rates < 50% in some studies
- Toxicity
 - 1-2% in adults

Rifamycins

- Inhibit DNA-dependent RNA polymerase
 - Active against non-replicating bacteria
 - Isoniazid only active against replicating bacteria
- Active against a broad array of bacteria (including MTB)
- Examples:
 - Rifampin
 - Rifabutin
 - Rifapentine







Rifampin – Adherence and toxicity

- Completion rates much higher
 - Up to 80% in one study
- Substantially less hepatotoxicity
 - 0.3% versus 1.4% for INH in one study

Rifamycins – other toxicity

- ❑ Hypersensitivity syndrome
 - “Flu-like” symptoms (fever, malaise, myalgias)
 - Not well-defined
- ❑ Anemia, thrombocytopenia
- ❑ Both more common with intermittent doses

Rifamycins – drug interactions

- | | |
|---------------------------------------|----------------------|
| ❑ Oral anticoagulants | ❑ Diazepam |
| ❑ Oral contraceptives | ❑ Digoxin (oral) |
| ❑ Cyclosporine | ❑ Diltiazem |
| ❑ Glucocorticoids | ❑ Disopyramide |
| ❑ Itraconazole | ❑ Doxycycline |
| ❑ Ketoconazole | ❑ Fluconazole |
| ❑ Methadone | ❑ Haloperidol |
| ❑ Midazolam or triazolam | ❑ Losartan potassium |
| ❑ Phenytoin | ❑ Nifedipine |
| ❑ Quinidine | ❑ Nortriptyline |
| ❑ Theophylline | ❑ Sulfonylureas |
| ❑ Verapamil | ❑ Tacrolimus |
| ❑ β -Adrenergic blocking agents | ❑ Tocainide |
| ❑ Chloramphenicol | |
| ❑ Clarithromycin | |
| ❑ Dapsone | |

Rifamycins – drug interactions

- ❑ **Check everything!**
- ❑ Oral contraceptives, coumadin, azole antifungals, and anti-rejection agents are common offenders
- ❑ Many antiretroviral agents (for HIV treatment) interact – always check everything
- ❑ Consult an expert for any interaction, especially when HIV meds are involved

Rifampin – Efficacy

- ❑ One study
- ❑ 679 Chinese men with silicosis randomized to one of three groups:
 - Rifampin for *three* months (3R)
 - Rifampin plus INH for three months (3HR)
 - Isoniazid for six months (6H)
 - Placebo

Hong Kong Chest Service. Am Rev Respir Dis. 1992 Jan;145(1):36-41.

Rifampin – Efficacy

- Development of active TB:
 - 3R: 12%
 - 3HR: 16%
 - 6H: 14%
 - Plac: 23%
- Risk reduction for 3R: 52%
- Risk reduction for 6H: 61%
(Pts all had silicosis, so rates were much higher)

Hong Kong Chest Service. Am Rev Respir Dis. 1992 Jan;145(1):36-41.

So where do we get “4 months” from?

- $6H < 12H \sim 9H$, so 9H is the recommendation
- $3R \sim 6H < 9H$, so....
- 4R is the recommendation

In other words, we have no direct efficacy data (yet) for four months of rifampin.

Rifapentine

- ❑ Similar to rifampin, but a longer half-life
- ❑ Initially approved for once-weekly therapy of active TB in the continuation phase
- ❑ Three studies of efficacy for treatment of LTBI (once per week in combination with isoniazid)

Rifapentine – efficacy

- ❑ 399 household contacts in Brazil
- ❑ Two groups:
 - Rifampin/pyrazinamide daily for two months (2RZ, control)
 - Rifapentine/isoniazid weekly for three months (3HP)
- ❑ Trial stopped early due to excess toxicity in Rif/PZA arm (the control group)
 - Not enough power to draw any conclusions
 - Only four cases developed
 - ❑ Three in 3HP arm
 - ❑ One in 2RZ arm

Schechter M. Am J Respir Crit Care Med. 2006 Apr 15;173(8):922-6.

Rifapentine – efficacy

- 1150 HIV+ patients in South Africa
 - Average CD4 between 500-600
- Four groups:
 - Rifapentine/isoniazid weekly for 3 months (3HP)
 - Rifampin/isoniazid 2x/week for 3 months (3HR)
 - Isoniazid daily throughout study (HHH...)
 - Isoniazid daily x 6 months (6H, control)
- Patients followed for 5 years

Martinson N et al. 39th IUATLD World Conference on Lung Health, late breaker abstract, Paris, 2008.

South Africa study – results

- No significant difference in efficacy between groups
- Continuous INH better years 1 & 2
 - Declined due to dropouts and toxicity years 3 & 4

Regimen	PY of follow up	RR	Comments
3HP	1242	1.05	1 MDR, 1 rif resistant
3HR	1279	1.06	
HHH....	582	0.71	1 MDR
6H	1182	Ref	

Martinson N et al. 39th IUATLD World Conference on Lung Health, late breaker abstract, Paris, 2008.

TB Trials Consortium Study 26 (PREVENT-TB)

- 8,000 “high-risk” patients in U.S., Brazil, Spain
 - Contacts, converters
 - HIV+ (very few)
 - Children 2 years and older
- Two arms:
 - Rifapentine/isoniazid weekly for 3 months by DOT (3HP-DOT)
 - Isoniazid daily for 9 months self-administered (9H-SAT)

Study 26 – results

- Both arms similar efficacy
 - 15 cases (0.43%) in 9H arm
 - 7 cases (0.19%) in 3HP arm
- Completion much higher with 3HP (80%)
- Toxicity slightly higher with 3HP (5% vs 3% in 9H)
 - Hepatotoxicity the same
 - “Excess” toxicity was hypersensitivity
 - (There is some evidence that it may have been over-reported.)

Study 26 – Some caveats

- DOT was used in the study, so there is no data on completion rates for self-administered therapy
 - Ten pills once per week – adherence could be very different
- Limited data on HIV+ patients
- No data yet on children <2 years

The practical stuff: Shorter course regimens for treating LTBI

Regimen 1 – 4R

- ☐ Rifampin 600 mg daily x 4 months
 - 6 months in children
- ☐ Most experience
- ☐ Can be used in children
- ☐ No data on efficacy
- ☐ Can be self-administered
- ☐ No intermittent option

Regimen 2 – 2RZ

- ☐ Rifampin 600 mg plus pyrazinamide 15-25 mg/kg daily for two months
- ☐ Good data on efficacy
- ☐ Kills people – not recommended

Regimen 3 – 3HR

- ❑ Rifampin 600 mg plus INH 300 mg for 3 months
- ❑ Commonly used in Europe
- ❑ Limited data on efficacy
- ❑ Can be self-administered
- ❑ No intermittent option

Regimen 4 – 3HP

- ❑ Rifapentine 900 mg plus INH 900 mg once per week for 3 months (12 doses)
- ❑ Limited experience, especially with HIV+ patients
- ❑ Solid data on efficacy



Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection

Weekly

December 9, 2011 / 60(48);1650-1653

Preventing tuberculosis (TB) by treating latent *Mycobacterium tuberculosis* infection (LTBI) is a cornerstone of the U.S. strategy for TB elimination (1,2). Three randomized controlled trials have shown that a new combination regimen of isoniazid (INH) and rifapentine (RPT) administered weekly for 12 weeks as directly observed therapy (DOT) is as effective for preventing TB as other regimens and is more likely to be completed than the U.S. standard regimen of 9 months of INH daily without DOT (2–5). This report provides CDC recommendations for using the INH-RPT regimen. The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients aged ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB). The new regimen also can be considered for other categories of patients when it offers practical advantages. Although the INH-RPT regimen was well tolerated in treatment trials, monitoring for adverse effects is recommended. Severe adverse effects should be reported to the Food and Drug Administration (FDA) and CDC.

3HP – CDC Recommendations (hot off the press)

- ☐ Equal alternative to 9H for the following:
 - Contacts
 - Recent converters
 - Old, healed (Class IV) TB
- ☐ Adults and children ≥ 12
 - Can be used in children 2-11 on a “case by case” basis
- ☐ HIV+ if healthy and on no ARVs
- ☐ Should not be used in pregnant women
- ☐ Should be given by DOT

Monitoring

- ❑ All patients on LTBI treatment with any regimen should be clinically monitored at least monthly.
- ❑ Rifampin only: Consider liver enzymes and CBC for the anyone meeting the following criteria:
 - HIV+
 - Regular alcohol use
 - Underlying liver disease
- ❑ If the patient is taking INH, use standard INH monitoring procedures, too.

Check for drug interactions

- ❑ Look them up!
- ❑ If the patient is HIV+ and on antiretrovirals, speak to one of the TB medical consultants and/or the patient's HIV physician before starting rifampin or rifapentine

“All of this is great, but aren’t these new drugs more expensive?”

- Well, yes.
- But if they prevent more TB, they may still *save money*.

Cost-effectiveness of LTBI treatment – a model

- Markov model of LTBI treatment
- Cohort of TB contacts at otherwise low risk of activation (i.e., HIV-negative, etc.)
- Four regimens considered:
 - 9H
 - 3HP (SAT and DOT)
 - 4R

Cost of LTBI drugs¹

Drug	Per pill	Per dose
Isoniazid 300 mg	\$0.03	\$0.03
Rifampin 300 mg	\$0.42	\$0.84
Rifapentine 150 mg	\$2.22	\$13.32
Pyridoxine 25 mg	\$0.01	\$0.01

¹NC Public Health Pharmacy Pricing

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¹NC Public Health Pharmacy Pricing

Other costs

- Monitoring = \$26.52 per visit
- DOT = \$24.08 per dose
- Cost of severe toxicity
 - Labs = \$164.80
 - Hospitalization (1%) = \$5,537.84

Known knowns and known unknowns

	9H	3HP-DOT	3HP-SAT	4R
Efficacy	93%	93%	93%	93%
Treatment-limiting toxicity	1.4%	5%	5%	0.35%
Adherence	53%	90%	87%	80%
Total therapy cost (incl. monitoring)	\$389	\$576	\$287	\$269

9H = Isoniazid daily for 9 months (SAT)

3HP = Isoniazid + rifapentine weekly for 3 months

4R = Rifampin for 4 month (SAT)

DOT = directly-observed

SAT = self-administered

A few other assumptions

Lifetime risk of activation	6%
Number of secondary cases/case	1.2
Cost of active TB	
6 months	\$13,000
9 months	\$13,783



ICER = Incremental cost-effectiveness ratio (in \$ per quality-adjusted life-years gained)

Definition

Dominate = be less expensive and more effective than (another regimen)

How wrong can we be? (Sensitivity analysis)

- Adherence*
 - 3HP-SAT
 - 3HP-SAT adherence can be as low as **66%** (base-case 87%) and still dominate 9H and/or 3HP-DOT

*Assume base case values for other parameters

Sensitivity analysis – continued

□ Efficacy*

- 4R can be 24% *less efficacious* than 9H and still dominate 9H

*Assume base case values for other parameters

Higher risk patients

- 3HP-DOT dominates all other regimens for HIV+ patients not on HAART
 - However, data on HIV+ patients is limited

Summary

- ❑ Rifamycins allow for shorter treatment of LTBI with better completion rates.
- ❑ Rifampin (4 months) is well-tolerated but has limited data on efficacy
- ❑ Rifapentine (with INH for 3 months) has good data on efficacy but should be given via DOT.
- ❑ Shorter course regimens using rifamycins are more effective and less expensive than isoniazid monotherapy
 - DOT may be justified for high-risk patients.

Questions?